Supplementary Materials

The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

Supplementary materials 1: Full search string.

PubMed

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR " local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help")

AND ("artificial intelligence"[MeSH] OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine"[MeSH] OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health")

AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors"[MeSH] OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Web Of Science

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR " local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help") AND ("artificial intelligence" OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine" OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health") AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors" OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Cochrane

ID	Search
#1	primary care
#2	ambulatory care
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#4	basic health care

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#6	basic healthcare
#7	day-to-day health care
#8	first aid
#9	initial medical care
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#22	primary care physician

#23	continuity of care
#24	medical station
#25	home care
#26	home assistance
#27	home help
#28	m-health
#29	mhealth
#30	mobile health
#31	ehealth
#32	e-health
#33	digital health
#34	artificial intelligence
#35	algorithms
#36	electronic prescribing
#37	Telehealth
#38	machine learning
#39	deep learning
#40	neural networks

#41	Machine Intelligence
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#43	telemedicine
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#52	medication prescription
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#55	drug dispensing error
#56	drug omission error
#57	drug monitoring error
#58	drug compliance error

#59	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#60	#28 OR #29 OR #30 OR #31 OR #32 OR #33#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
#61	#44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 #57 OR #58
#62	#59 AND #60 AND #61

Supplementary materials 2: Additional characteristics of the included studies

Author, year country	Name of the intervention	Intervention description	Population targeted	Setting	Type of evaluated population	Type of patient or health care specialists	Duration of the intervention
Berner ES, 2006, US	The Intervention Rule (Nonsteroidal Anti-inflammatory Drug Gastrointestinal RISK)	"The Intervention Rule assessed six established risk factors for GI complications from NSAIDs: age, self-assessed health status, diagnosis of rheumatoid arthritis, steroid use, a history of GI hemorrhage or hospitalization for ulcer, and symptoms with NSAIDs.Users enter all six elements into the PDA via pull-down menus and tap a submit button on the PDA screen to receive the score and recommendation."	physicians, patients	primary care residency	at risk	Patients at risk of Gastrointestinal complications	6 months
Fried TR, 2017, US	Tool to Reduce Inappropriate Medications (TRIM)	TRIM (a web tool) extracts data about medications and chronic conditions from the EHR. These data serve as input for automated algorithms identifying medication reconciliation discrepancies, PIMs, and potentially inappropriate regimens.	patients	Primary care clinics	at risk	Patients aged 65 years and older prescribed ≥ 7 medications	12 months
Muth C,2018, Germany	Prioritising Multimedication in Multimorbidity (PRIMUM)	The healthcare assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision support system, the general practitioner optimised medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.	physicians	General practitioners ambulatories	at risk	Patients aged 60 years and older, with ≥3 chronic conditions, under pharmacological treatment with ≥5 long-term drug prescriptions with systemic effects	9 months
Gurwitz JH, 2008, US and Canada	Computerized provider order entry with clinical decision support system to prevent adverse drug events	For residents on the intervention units, the alerts were displayed in a pop-up box to prescribers in real time when a drug order was entered. The pop-up boxes were informational; they did not require specific actions from the prescriber and did not produce or revise orders automatically	physicians	Long-term care setting	at risk	In-patients	12 months
Rieckert A, 2020, Germany	Polypharmacy in chronic diseases: reduction of inappropriate medication and adverse drug events in older populations by	The intervention consisted of a computerised decision support tool providing a comprehensive drug review (see appendix figs 1a and 2a) generated from patient data recorded in the electronic case report form.	Physicians	General practitioners ambulatories	at risk	Adults aged 75 years and older using eight or more drugs on a regular basis	24 months

	electronic decision support (PRIMA-eDS)						
Tamblyn R, 2008, Canada	prescribing alerts generated by computerized drug decision support (CDDS)	Effectiveness of two approaches to medication alert customization: on-physician-demand versus computer-triggered decision support.	physicians, patients	ambulatory care	not at risk	Patients with at least one prescription by the study physician.	6 months
Tamblyn R,2019, Canada	The medical office of the 21st century (MOXXI)	Physicians in the CDS group obtained information on each patient by downloading updates of dispensed prescriptions from the RAMQ drug-insurance program. These data were integrated into the patient's health record and categorized as having been prescribed by the study physician or by another physician. Alerts were instituted to identify 159 clinically relevant prescribing problems in the elderly, a list established previously by expert consensus:	physicians	Primary care physicians ambulatory	not at risk	Patients aged 66 years and older	13 months
Bhardwaja B, 2011, US	The Drug Renal Alert Pharmacy (DRAP) Program	Patient-specific Clcr data were transferred to the Pharmacy Information Management System (PIMS), enabling PIMS to trigger an alert when a potential medication error was detected—that is, when a target drug was ordered for a patient with a drug-specific Clcr cutoff value. In contrast to alerts that notify the provider at the point of prescription entry, when a potential error was detected in our system, the alert would notify the pharmacist and stop the dispensing process by preventing the prescription label from being printed. In lieu of the prescription label, a medication decision guide was printed for the pharmacist that outlined the process for intervening on the alert. The pharmacist then confirmed if there was an error by using the medication guide, and if needed, contacted the prescribing physician to discuss the potential problem. All pharmacist activities were electronically documented in PIMS.	pharmacists	ambulatory pharmacies	at risk	Patients at least 18 years old, with an estimated creatinine clearance of 50 ml/minute or lower, and not receiving dialysis	15 months

Tamblyn R,2012, Canada	MOXXI	Intervention physicians received information about patient-specific risk of injury computed at the time of each visit using statistical models of nonmodifiable risk factors and psychotropic drug doses. Risk thermometers presented changes in absolute and relative risk with each change in drug treatment. Control physicians received commercial drug alerts.	physicians	Family physicians ambulatory	not at risk	Patients aged 65 and older who were prescribed psychotropic medication	12 months
Chrischilles, 2014, US	Iowa PHR (personal health record)	Iowa PHR is a web-based application that features a tabbed interface design. Users can enter, view, and print their current and past medicines, allergies, health conditions, and health event tracking over time. An embedded tutorial video provides assistance with the system. Iowa PHR displayed a message when a user entered a medication with an associated ACOVE-3 safety concern. The messages were displayed in three levels of increasing detail and complexity to facilitate tiered information take-up: a brief alert containing the basic reason for concern, a summary level that included recommended actions, and a detailed explanation of the alert.	patients	patient's home	not at risk	Adults age 65+	7 months
Clyne B,2015, Ireland	OPTI-SCRIPT study (Optimizing Prescribing for Older People in Primary Care, a cluster-randomized controlled trial)	web-based pharmaceutical treatment algorithms for GPs that provided evidencebased alternative treatment options to PIP drugs, and tailored patient information leaflets	physicians, patients	Ambulatory care	not at risk	70 yo patients and older	11 months
Holt, TA et al, 2017, England	Effectiveness of a software tool (AURAS-AF [Automated Risk Assessment for Stroke in Atrial Fibrillation]) designed to identify people at risk of stroke, but not	Screen reminders appeared each time the electronic health records of an eligible patient was accessed until a decision had been taken over OAC treatment	patients	primary care practice	at risk	Patients with Atrial fibrillation but not receiving treatment with Oral Anti Coagulants to prevent stroke	6 months

	receiving treatment, during routine care						
Lopez-Picazo, JJ, 2011, Spain	OMI-ap + PRISMAp	3 different intervention group: delivery of the interaction report (report group), implementation of clinical educational sessions using the report data (session group), and faceto-face interviews between each family physician and a pharmacist who was specially trained to present the results of the report (face-to-face group)	physicians	Primary care centres	not at risk	All patients in the practice who were older than 14 years of age if they were taking more than 1 drug and therefore at risk for drug interactions	15 months
Matsuyama JR, (1993) France	Medication-event monitoring system (MEMS III)	The microprocessor in the cap records each opening as a presumptive dose, storing the date and time for later retrieval by a microcomputer.	patients	Ambulatory care	at risk	Patients with poor to fair metabolic control of diabetes mellitus were enrolled.	11 months

Supplementary materials 3: Results of quality assessment.

Author(year)	1	2	3	4	5	6	7	9	10	11	12	13	14	Overall
Berner ES, 2006	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Bhardwaja B, 2011	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	G
Chrischilles, 2014	Y	N	NR	NR	NR	Y	N	N	NR	Y	N	Y	Y	P
Clyne, B,2015	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	F
Fried TR, 2017	Y	Y	Y	NR	N	Y	N	N	NR	Y	N	Y	NR	P
Gurwitz JH, 2008	Y	Y	Y	NR	NR	Y	Y	N	N	NR	N	NR	NR	P
Holt TA, 2017	Y	Y	Y	NR	Y	Y	NR	Y	NR	Y	Y	Y	Y	F
Lopez-Picazo JJ, 2011	Y	Y	Y	N	Y	Y	NR	NR	NR	Y	N	Y	Y	F
Matsuyama JR, 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	G
Muth C,2018	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Rieckert A, 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	G
Tamblyn R, 2008	Y	Y	N	N	NR	Y	Y	N	Y	N	Y	Y	NR	P
Tamblyn R,2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	G
Tamblyn R,2019	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	F

Abbreviations: Y, yes; N, no; NR, not reported; G, good quality; F, fair quality, P, poor quality.

Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs)

Signalling questions:

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?

2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?

3. Was the treatment allocation concealed (so that assignments could not be predicted)?

4. Were study participants and providers blinded to treatment group assignment?

5. Were the people assessing the outcomes blinded to the participants' group assignments?

6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?

9. Was there high adherence to the intervention protocols for each treatment group?

10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?

11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?

12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?

13. Were outcomes reported or subgroups analysed prespecified (i.e., identified before analyses were conducted)?

14. Were all randomized participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?